Structure and Stereochemistry of Adducts of Ergosterol with Dihalocarbenes[1]

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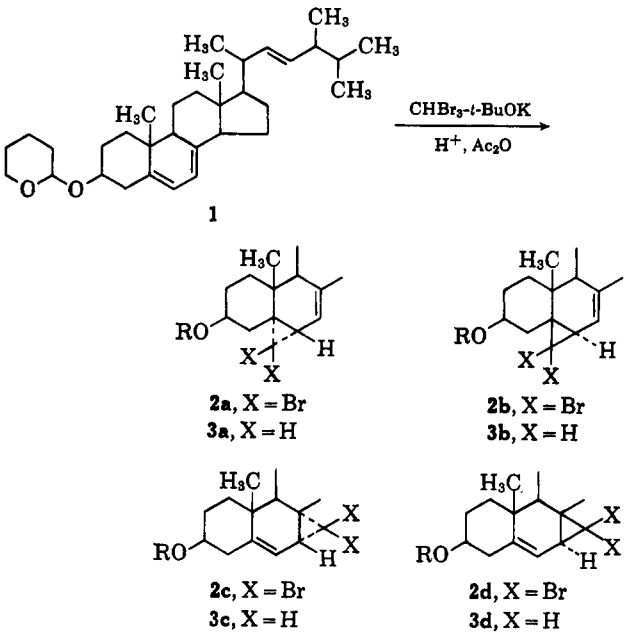
Ergosteryl tetrahydropyranyl ether (1) reacts with dichlorocarbene and with dibromocarbene to give the 5α,6α adducts, for example, **2a**, convertible to the 5α,6α-methylene compound **3a**. The ultraviolet spectrum of **2a** indicated efficient conjugation of the cyclopropane ring with the adjacent double bond and this suggested that reduction with lithium aluminum hydride might proceed with participation of the 7,8 double bond. This expectation was realized and the reduction product was characterized as having a 6,7 double bond and a 5α,8α-methylene bridge (**9a**).

When this work was undertaken no previous study had been made in the steroid series of the interesting reaction of olefins with dihalocarbenes to give cyclopropanes[2] discovered by Doering and Hoffmann.[3] However, three reports are now on record with results and conclusions which should be considered in connection with those to be presented. Knox, *et al.*,[4] found that an isolated 5,6 double bond is inert to dichlorocarbene but adds difluorocarbene to give a *gem*-difluorocyclopropane regarded as having the 5β,6β orientation. Of the arguments presented in support of this assignment, the strongest seems to be the observation that in the n.m.r. spectrum the C-10 methyl group has a split signal attributed to coupling with a spatially close fluorine atom.[5] The failure of the bulky dichlorocarbene to add to an isolated 5,6 double bond is thus attributed to shielding by the C-10 methyl group against β attack. The Syntex group[4] found further that $\Delta^{3,5}$ steroid dienes add dichlorocarbene to the 3,4 position and assigned to the adducts the 3α,4α configuration. On the other hand $\Delta^{3,5}$-19-norsteroids add dichlorocarbene at the 5,6 position to give cyclopropanes assigned the 5β,6β orientation. However, Font[6] investigated the addition of dibromocarbene to 17β-acetoxy-3-ethoxy-$\Delta^{3,5}$-estradiene, a 19-norsteroid and isolated (after hydrolysis to the 3-ketone) both the 5α,6α and the 5β,6β adducts. Cookson and coworkers[7] assigned the α orientation to 2,3-dibromocarbene adducts on the ground of the rule of rear at tack.[8]

The preparation and characterization of 5,6 adducts was the particular aim of the present work. When the double bond of cholesterol proved to be resistant to dichloro- and dibromocarbene, attention was directed to ergosterol, the 5,6 double bond of which is known to be particularly reactive.[9] Reaction of ergosteryl tetrahydropyranyl ether (1) with dibromocarbene gave in 40% yield a bromine-containing product which on hydrolysis[10] and acetylation gave an acetate, m.p. 169–170°, having the composition of an ergosteryl acetate dibromomethylene adduct. An infrared band at 10.3 μ indicated the presence of the side-chain double bond[11] and the four-band ultraviolet spectrum characteristic of the homoannular diene system was missing. The ultraviolet spectrum shows moderate absorption at 218 mμ (ε 9000) indicative of a well-conjugated vinylcyclopropyl grouping[12,13]; it is at a wave length much longer than that expected for an isolated double bond[14] and shorter than for any conjugated steroidal diene.[15] The n.m.r. spectrum shows vinylic hydrogens at τ 4.8 (2H, side chain) and 4.6 (1H, C-6 or C-7). The product, therefore, must have one of the four vinylcyclopropyl structures, **2a–d**.



Reduction of the adduct as the free alcohol 2 (R = H) by hydrogenation over W-2 Raney nickel was incomplete but a halogen-free product **3** was isolated in 60–70% yield. The spectral properties of **3** indicate that the vinylcyclopropyl system and the side-chain double bond are preserved: ultraviolet absorption

(1) Dedicated to Professor Louis F. Fieser on the occasion of his 66th birthday for his distinguished contributions to teaching, research, and writing in organic chemistry.

(2) See review by W. E. Parham and E. E. Schweizer, *Org. Reactions*, **13**, 55 (1963).

(3) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(4) L. H. Knox, E. V. Velarde, S. M. Berger, and D. H. Cuadriello, *Chem. Ind.* (London), 860 (1962); L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 1851 (1963).

(5) A. D. Cross and P. W. Landis, *ibid.*, **84**, 3784 (1962).

(6) A. B. Font, *Bull. soc. chim. France*, 419 (1964).

(7) R. C. Cookson, D. P. G. Hamon, and J. Hudec, *J. Chem. Soc.*, 5782 (1963).

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 14.

(9) See ref. 8, pp. 112, 120.

(10) C. W. Greenhalgh, H. B. Henbest, and E. R. Jones, *J. Chem. Soc.*, 1190 (1951).

(11) J. H. Turnbull, D. H. Whiffen, and W. Wilson, *Chem. Ind.* (London), 626 (1950).

(12) I. M. Klotz, *J. Am. Chem. Soc.*, **66**, 88 (1944).

(13) J. W. Rowe, A. Melera, D. Arigoni, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **40**, 1 (1957).

(14) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(15) See ref. 8, p. 15.

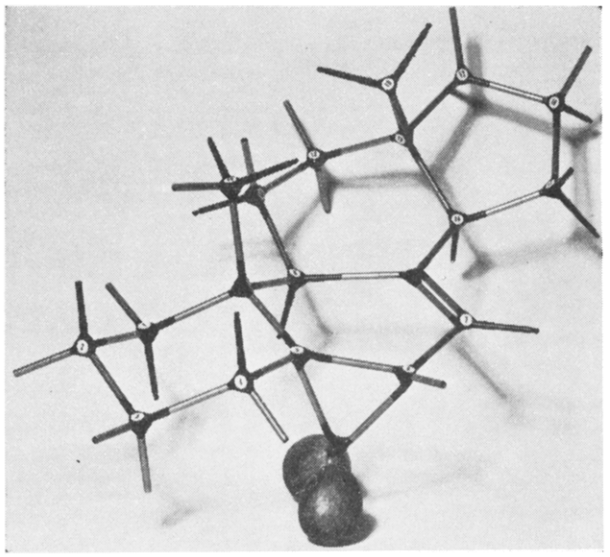


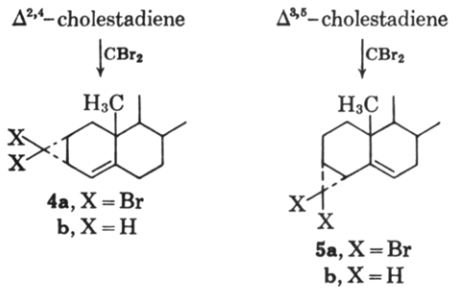
Figure 1.—A Fieser model of **2a**.

at 227 mμ (ε 6000); n.m.r. bands in the olefinic region identical with those of **2**. Of interest is the fact that a group of bands above τ 9.5 expected for the cyclopropyl methylene protons[16] does not appear. The adjacent double bond may have deshielded the cyclopropyl methylene protons and caused a downfield shift.[17] If so, removal of the double bond from conjugation with the ring, either by saturation or bond migration, should result in appearance of the high-field protons. With this objective, and for location of the nuclear double bond, the ester **3** (R = Ac) was hydrogenated over 10% palladium on carbon in ethyl acetate to saturate the double bond in the side chain and to effect either isomerization of a 7,8 double bond to a tetrasubstituted 8,14 double bond (**3a** or **3b**)[18] or saturation of a 5,6 double bond (**3c** or **3d**). The product of hydrogenation was found to be a 22,23-dihydro derivative having no olefinic protons (n.m.r.) and to give positive tetranitromethane[19] and Tortelli–Jaffé[20] color tests, indicating the presence of a tetrasubstituted double bond. Therefore **2** and the halogen-free product **3** are 5,6 adducts with a 7,8 double bond. The same conclusion was arrived at by isomerization of the 7,8 double bond to the 8,14 position by the action of gaseous hydrogen chloride.[21] The product showed the expected cyclopropyl methylene proton signals in the n.m.r. at τ 9.7.

Conclusive evidence for 5,6 addition was obtained by adding dibromocarbene to $\Delta^{5,7}$-cholestadien-7-*d*-3β-ol.[22] The ultraviolet spectrum of the dienol is identical with that of ergosterol, and the tetrahydropyranyl ether shows only one olefinic proton (C-6) in the n.m.r. which disappears on reaction with dibromocarbene. Dichlorocarbene, generated from chloroform or from sodium trichloroacetate, by the procedure of Fieser and Sachs,[23] also adds to the 5,6 double bond of **1** in the same steric sense, since reductive removal of the chlorine atoms from the adduct gave a product identical with that obtained from the dibromocarbene adduct.

The next problem was that of the stereochemistry of the 5,6 adducts. A clue to a scheme for establishment of the configuration of adducts **2** and **3** was suggested by their ultraviolet spectra. As already noted, the wave length and intensity of the band at 218 mμ for **2** (and that at 227 mμ for **3**) reveal a great deal of interaction between the 7,8 double bond and the cyclopropane ring.[24] The degree of interaction is dependent upon the angular relationship between the plane of the cyclopropane ring and the plane of the double bond; interaction is at a maximum when the two planes are perpendicular to one another.[24] A Fieser model[25] of the α adduct **2a** (Figure 1) shows a rigid geometry for ring B with the cyclopropane ring held in a plane close to perpendicular with the plane of the 7,8 double bond. This relationship is not distinctive of the α adduct **2a**, for it is shown as well in a model of the β adduct **2b**. It seemed desirable to test the suggested correlation between ultraviolet spectrum and geometry of the vinylcyclopropyl system by examining adducts of $\Delta^{2,4}$- and $\Delta^{3,5}$-cholestadiene.

$\Delta^{2,4}$-Cholestadiene, prepared by dehydration of cholesterol[26] or from cholestanone,[27] adds one dibromocarbene species to give the 2α,3α adduct **4a**.[28] $\Delta^{3,5}$-Cholestadiene[29] under the same conditions gave the



3α,4α adduct **5a**. The structures were determined easily from the presence in the n.m.r. spectrum of each adduct of absorption for only one olefinic proton. Assignment of the α configuration rests upon the known relationship between the orientation of a substituent in ring A or B and the position of the n.m.r. signal for the C-10 methyl group.[4,30–32] By virtue of having a *cis* relationship a β substituent is expected to cause a

(16) L. M. Jackman, "Applications of N.m.r. Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 52.

(17) V. Georgian, J. F. Kerwin, M. E. Wolff, and F. F. Owings, *J. Am. Chem. Soc.*, **84**, 3595 (1962).

(18) See ref. 8, p. 273.

(19) A. Werner, *Ber.*, **42**, 4325 (1909).

(20) I. M. Heilbron and F. S. Spring, *Biochem. J.*, **24**, 133 (1930).

(21) See ref. 8, p. 114.

(22) Prepared by the procedures for the conversion of cholesterol to 7-dehydrocholesterol but using lithium aluminum deuteride for reduction of 7-ketocholesteryl acetate to the 3β,7β-diol: L. F. Fieser, M. Fieser, and R. N. Chakravarti, *J. Am. Chem. Soc.*, **71**, 2229 (1949); G. A. D. Haslewood, *Biochem. J.*, **33**, 454 (1939).

(23) L. F. Fieser and D. H. Sachs, *J. Org. Chem.*, **29**, 1113 (1964).

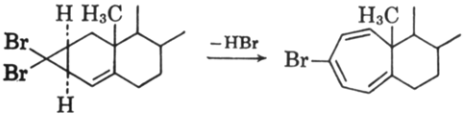
(24) E. M. Kosower and M. Ito, *Proc. Chem. Soc.*, 25 (1962).

(25) L. F. Fieser, *J. Chem. Ed.*, **40**, 457 (1963).

(26) E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

(27) Following the procedure for the preparation of 17α-methyl-$\Delta^{2,4}$-androstadien-17β-ol: B. Berkoz, A. D. Cross, M. E. Adame, H. Carpio, and A. Bowers, *ibid.*, **28**, 1976 (1963).

(28) A by-product isolated from the reaction mixture is considered, tentatively, to be a cycloheptatriene on the basis of its elemental analysis and n.m.r. and ultraviolet spectra.



(29) A. E. Sobel and M. J. Rosen, *J. Am. Chem. Soc.*, **63**, 3536 (1941).

(30) G. Slomp, Jr., and B. R. McGarvey, *ibid.*, **81**, 2200 (1959).

(31) J-C. Jacquesy, J-M. Lehn, and J. Levisalles, *Bull. soc. chim. France*, 2444 (1961).

(32) R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1960).

larger shift of the n.m.r. signal for the C-10 methyl group than an α substituent.[30] The shift varies with the nature of the substituent.[31] Data for the 2,3 and 3,4 adducts, as well as for the corresponding methylene compounds and monohalomethylene compounds, are listed in Table I. The monohalomethylene compounds were prepared by partial reduction of the corresponding dihalomethylene adducts with W-2 Raney nickel or palladium on carbon in the presence of alkali; their structures were established by n.m.r. (one-proton absorption centered at τ 6.6 for a proton on the carbon carrying the halogen) and further reduction to the methylene compound. The fact that variation in the nature of the substituent (CH_2, CCl_2, CBr_2) caused no shift in the position of the C-10 methyl group signal strongly favors assignment of the α configuration to the 2,3 and 3,4 adducts. Similar evidence could not be used to establish the configuration of the 5,6 adducts **2** and **3** since the vinylcyclopropyl system in these adducts acts as a unit and changes in the cyclopropane ring affect the system as a whole and consequently affect the position of the C-10 methyl group signal whether the 5,6 adduct is α or β. Neither adduct **4** nor adduct **5** exhibits in the ultraviolet any absorption maximum above 210 mμ. Moreover, the n.m.r. spectra of **4b** and **5b** show absorptions characteristic for cyclopropyl methylene protons at τ 10.1 and 9.9, respectively. These spectral observations indicate a much smaller degree of conjugation between the cyclopropane ring and the neighboring double bond. The flexibility of ring A allows the cyclopropane ring to assume an orientation where the nonbonded interactions are least. Models show that in such an orientation the plane of the cyclopropane ring is far from perpendicular to the plane of the double bond.

TABLE I

POSITION OF THE N.M.R. SIGNAL OF THE C-10 METHYL GROUP

	C.p.s.[a]
Δ^4-Cholestene	60
2,3-Methylene-Δ^4-cholestene	62
2,3-Monochloromethylene-Δ^4-cholestene	62
2,3-Monobromomethylene-Δ^4-cholestene	62
2,3-Dichloromethylene-Δ^4-cholestene	62
2,3-Dibromomethylene-Δ^4-cholestene	62
3,4-Methylene-Δ^5-cholestene	53
3,4-Monochloromethylene-Δ^5-cholestene	53
3,4-Dichloromethylene-Δ^5-cholestene	53
3,4-Dibromomethylene-Δ^5-cholestene	53

[a] Relative to tetramethylsilane at 0 c.p.s.

The finding that in the ergosterol 5,6 adducts the cyclopropane ring is held in an orientation such that interaction with the double bond is extensive suggested the possibility of utilizing participation by the double bond in a reaction on the cyclopropane ring which might afford a product suitable for establishing the configuration of the 5,6 adducts. A reaction which seemed promising was reduction of the 5,6-dibromomethylene adduct **2** with lithium aluminum hydride. This reagent usually effects complete reduction only of reactive halides such as allyl halides,[33] where the halogen is activated by a double bond. Recently, Story[34]

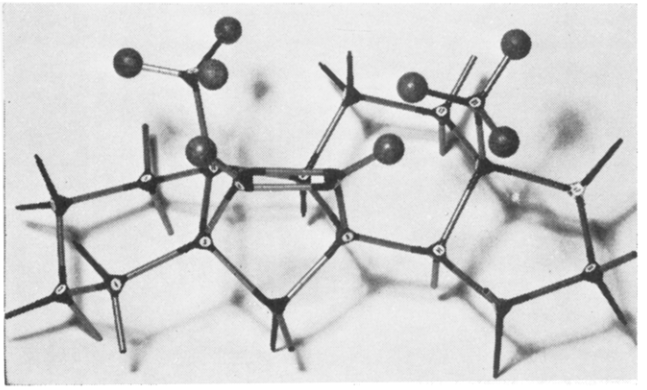
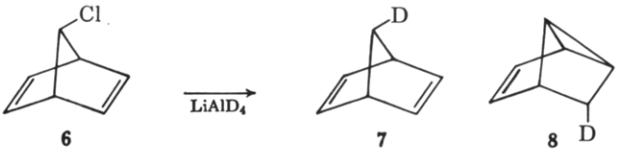


Figure 2.—A Fieser model of 9a.

found that 7-chloronorbornadiene (**6**) is reduced by lithium aluminum deuteride to a mixture of norbornadiene **7** and the tricyclic hydrocarbon **8**, which



provides clear evidence of the participation of the double bond during the reaction. In the hope of similar participation of the 7,8 double bond a solution of the 5,6-dibromomethylene adduct, as the tetrahydropyranyl ether, was stirred with lithium aluminum hydride in diethyl ether for 2 days. Chromatography as the acetate afforded two halogen-free products. One (5%) proved to be the 5,6-methylene compound **3**, and the other (90–95%) a structural isomer. This substance (**9**) shows no ultraviolet absorption maximum above 210 mμ. The n.m.r. spectrum indicated the absence of an isolated cyclopropane ring but showed a well-defined two-proton quartet in the olefinic region, τ 4, an AB system[35,36]; additional splitting of the quartet is not evident. The peaks are sharp enough to exclude the presence of interacting protons on carbons adjacent to the unsaturated carbons. One way to account for this observation is to assume the presence of fully substituted carbon atoms on each side of the double bond, as in formula **9a** or **9b** (see Scheme I).

That the ring-B double bond originally at 7,8 is, in **9**, at the 6,7 position was established by experiment in the 7-dehydrocholesterol series with the 5,6-dibromocarbene adduct labeled with deuterium at C-7. This was reduced to a product completely analogous to **9**, which shows a one-proton singlet in the olefinic region, τ 4.0, indicative of an olefinic proton at C-6.

Evidence for the [2.2.1]bicyclo system was obtained as follows (only the 5α,6α, or **a** series is formulated). The 22,23 double bond was eliminated by hydrogenation and the product was treated with lithium aluminum hydride to give a rearrangement product analogous to **9a**. The unsaturated alcohol **11** was converted to the 6,7-epoxide **12**, which on reduction gave a mixture of the two alcohols. Oxidation gave the two diketones, **13** and **14**, which were separated by chromatography. One had infrared bands at 5.70 and 5.80 μ, the

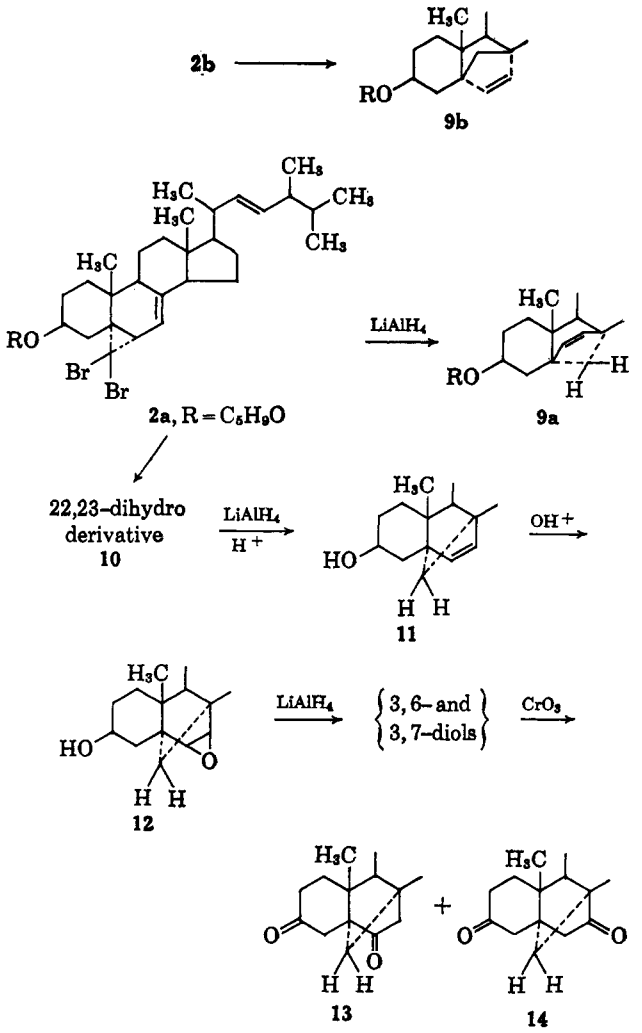
(33) N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 889.

(34) P. R. Story, *J. Am. Chem. Soc.*, **83**, 3347 (1961).

(35) See ref. 16, p. 89.

(36) The quartet is also shown by the lithium aluminum deuteride dehalogenation product of **2a**, an indication that no deuterium has been introduced at C-6 and C-7.

SCHEME I

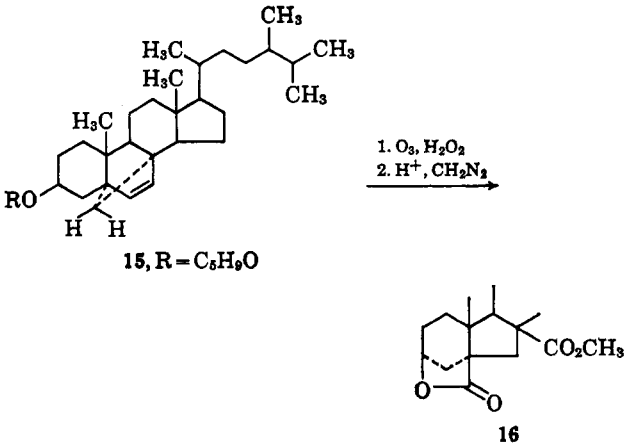


other at 5.65 and 5.85 μ. The bands at 5.65 and 5.70 μ show the presence in each component of a carbonyl group in a five membered ring.[37]

The evidence so far presented establishes the presence in **9** of a 5,8-methylene bridge, but the problem of the configuration of this bridge remained to be solved. The 5α,6α-dibromomethylene adduct would give a 5α,8α-methylene bridge (**9a**), the 5β,6β adduct a 5β,8β bridge (**9b**). The first indication of an α configuration came from examination of the n.m.r. spectrum. Two groups of bands were considered specifically: a quartet attributed to the 6,7 double bond protons, and the angular methyl signals. Molecular models (Figure 2) demonstrate that the different shieldings experienced by the olefinic protons and the shifts observed for the C-13 methyl group resonance on hydrogenation of the 6,7 double bond are best explained by the 5α,8α bridge configuration **9a**. Examination of a model for the alternative configuration with a β bridge show that the double bond is at the back of the molecule and isolated from the other electronic centers and hence that the C-6 and C-7 olefinic protons would not have chemical shifts different enough to produce a quartet. Indeed the n.m.r. spectrum of 3α-acetoxy-Δ^6-cholenate, a reasonable model compound, shows only one peak at τ 5.5 for the C-6 and C-7 protons.

(37) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 148.

Unequivocal chemical evidence of an α bridge was arrived at as follows. The 22,23-dihydro derivative of **9**, as the tetrahydropyranyl ether **15**, was ozonized[38] and the ozonide was decomposed to a diacid with hydrogen peroxide. A solution of the diacid in methanol



was treated with a few drops of hydrochloric acid. Esterification with diazomethane and chromatography of the resulting mixture of methyl esters gave oily fractions which showed in the infrared carbonyl region two distinct bands. The band at 5.65 μ is a definite indication of a γ-lactone group,[39] as in **16**. Formation of a γ-lactone is possible only if the carboxyl group produced at C-5 and the 3β-hydroxyl are on the same side of the molecule. Therefore, the starting olefin **15** must have the 6,7 double bond in the same (β) orientation as the C-3 oxygen function. The 5,6-dihalomethylene adducts of ergosterol are thus shown to be α adducts.[40]

Lithium aluminum hydride reduction of the 2α,3α-dibromomethylene adduct of $\Delta^{2,4}$-cholestadiene (**4a**), and of the dichloromethylene derivative, gave no products of rearrangement. Reduction in this case was incomplete and the products isolated were the 2α,3α-methylene and 2α,3α-monohalomethylene derivatives. Reduction of the 5α,6α-dibromo- and dichloromethylene adducts with lithium–*t*-butyl alcohol–tetrahydrofuran or sodium in liquid ammonia was complete and gave a mixture of the 5α,6α-methylene derivative (90%) and the 5α,8α-methylene derivative (8%).

Experimental[41]

Ergosteryl Tetrahydropyranyl Ether (1).—Dihydropyran (15 ml., purified by distillation over potassium hydroxide pellets) was added to a slurry of ergosterol (25 g., Matheson Coleman and

(38) J. W. Cornforth, G. D. Hunter, and G. Popjak, *Biochem. J.*, **54**, 595 (1953).

(39) See ref. 37, p. 186.

(40) The apparent variance of these results with those obtained by Knox, *et al.*, is explainable if the mechanism of addition of carbenes to double bonds be considered to pass through charged intermediates where one new carbon–carbon bond is formed first [P. S. Skell and A. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956)]. In the case of addition to the 5,6 double bond of a Δ^5 or a $\Delta^{5,8}$ steroid, maximum orbital overlap is achieved when the bond generated is 6β axial (see Knox, Velarde, Berger, Cuadriello, Landis, and Cross, ref. 4, footnotes 27 and 28) and the positive charge at C-5 is stabilized by virtue of being tertiary in one case and both tertiary and allylic in the other. The end product is then the 5β,6β adduct. In the case of $\Delta^{5,7}$-dienes, the corresponding intermediate would have a 5α axial carbon–carbon bond and a stabilized allylic carbonium ion at C-6.

(41) Infrared spectra were recorded, in the solid phase (KBr), on a Perkin-Elmer Model 21 spectrophotometer, and, in Nujol or neat, on a Perkin-Elmer Model 137 Infracord spectrophotometer. Ultraviolet spectra were

Bell) in dichloromethane (100 ml.) and followed by dropwise addition of phosphorus oxychloride (0.2 ml.). The mixture was frequently agitated and cooled to keep its temperature below 35°. In a few minutes the solid dissolved completely to a yellow-green solution. The solution was allowed to cool to room temperature, then transferred to a separatory funnel, diluted with diethyl ether (400 ml.), and washed twice with 5% sodium bicarbonate and once with saturated sodium chloride solution. The light orange organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The solid residue was triturated with cold acetone (30 ml.), filtered, and washed with more acetone to give a white crystalline solid (22 g.); m.p. 150–155°; α_D −75°; $\lambda^{cyclohexane}$ 295, 283 (ϵ 11,500), 270, and 264 mμ; ν_{KBr} 8.8, 9.0 (ether),[42] and no hydroxyl band around 2.8 μ; τ 6.4 (3H, protons on carbon joined to oxygen by a single bond), and 5.2 (1H, proton on carbon joined to two oxygens). The product was used in the subsequent reactions without further purification. Attempts to recrystallize it resulted in partial hydrolysis to the alcohol. The acetone-washed ether was found to be satisfactory.

Concentrated hydrochloric acid (0.1 ml.) was added to a suspension of the tetrahydropyranyl ether (1 g.) in 95% ethanol (30 ml.). Heating the mixture on the steam bath gave a clear solution from which ergosterol was obtained by cooling.

5α,6α-Dibromomethylene-Δ^{7,22}-ergostadien-3β-ol Tetrahydropyranyl Ether (2a).—Ergosteryl tetrahydropyranyl ether (10 g.) was dissolved in *n*-pentane (500 ml.) and the solution was filtered to remove the suspended ergosterol. To the clear solution, at 0–25°, was added potassium *t*-butoxide (10 g.), the mixture was stirred, and bromoform (10 g. in 30 ml. of *n*-pentane) was introduced (dropwise) over a period of 30 min.[3] The brown reaction mixture was stirred for 2 hr. and filtered through a sintered-glass funnel containing alumina, and the filtrate was evaporated to a light brown semisolid. The residue was treated with cold diethyl ether and recrystallized from isopropyl ether to give 4.0 g. of short feathery needles; m.p. 143–146°; α_D +12°; $\lambda^{cyclohexane}$ 218 mμ (ϵ 9000); ν_{KBr} 8.8, 9.0 (ether), and 10.3 μ (side-chain double bond)[11]; τ 4.8 (2H, side-chain olefinic protons) and 4.6 (1H, C-7 proton). Repeated recrystallization or chromatography over alumina resulted in partial hydrolysis to the corresponding alcohol. For analytical purposes the acetate was prepared as follows. The ether (1 g.), 95% ethanol (80 ml.), and concentrated hydrochloric acid (0.2 ml.) were heated on the steam bath until solution was complete. Cooling to room temperature deposited feathery needles of an alcohol (0.3 g.); m.p. 158–159°, λ^{EtOH} 218 mμ (ϵ 9000), ν_{KBr} 2.8 μ (hydroxyl) and no ether bands at 8.8 and 9.0 μ. The filtrate was diluted with water to give an additional 0.5 g. of the alcohol. The alcohol (0.7 g.), pyridine (30 ml.), and acetic anhydride (15 ml.) were mixed and kept at room temperature for 15 hr. The reaction mixture was poured over ice and the precipitate was filtered and recrystallized from acetone to give silky needles of the acetate of **2a** (0.6 g.); m.p. (analytical sample) 169–170°, α_D +10°, $\lambda^{cyclohexane}$ 218 mμ (ϵ 9000), ν_{KBr} 5.75 μ (acetate), τ 4.8 (2H, side-chain double-bond protons) and 4.6 (1H, C-7 proton).

Anal. Calcd. for $C_{31}H_{46}Br_2O_2$ (610.51): C, 60.98; H, 7.59; Br, 26.18. Found: C, 60.91; H, 7.51; Br, 26.33.

5α,6α-Dichloromethylene-Δ^{7,22}-ergostadien-3β-ol Acetate. A.—Use of chloroform (10 g.) in place of bromoform in the above experiment resulted in 4.5 g. of needles, m.p. 155–160°, α_D +11°; all spectral properties corresponded to those of the dibromomethylene adduct **2a** (R = tetrahydropyranyl). Hydrolysis of the ether to the alcohol, m.p. 182–183°, and acetylation gave needles (from acetone); m.p. 155–157°, α_D +9°.

Anal. Calcd. for $C_{31}H_{46}Cl_2O_2$ (521.59): C, 71.36; H, 8.89; Cl, 13.59. Found: C, 71.26; H, 8.80; Cl, 13.45.

B.—Ergosteryl acetate (5 g.), sodium trichloroacetate (20 g.), tetrachloroethylene (20 ml.), and diglyme (5 ml.) were refluxed until all the sodium trichloroacetate lumps were decomposed to finely divided sodium chloride.[23] The brown reaction mixture was steam distilled to remove tetrachloroethylene. The remaining semisolid was extracted with diethyl ether. Drying and evaporation of the ether afforded a product which, when washed with ethyl acetate and filtered, gave crystalline solid (1.5 g.) identical with the acetate obtained in A.

5α,6α-Methylene-Δ-^{7,22}-ergostadien-3β-ol Acetate (3a, R = Ac).—Dibromomethylene adduct **2a** (R = H, 513 mg.), absolute ethanol (50 ml.), potassium hydroxide (0.5 g. in 1 ml. of distilled water), and 1 teaspoonful of W-2 Raney nickel slurry[43] were stirred under hydrogen at atmospheric pressure and room temperature for 24 hr. The catalyst was filtered off and the filtrate was diluted with water and extracted with diethyl ether. Evaporation of the dried ether extracts gave a halogen-containing solid which was acetylated. Repeated chromatography of the acetate mixture (m.p. 185–195°) gave two fractions, 130 mg. of unreacted **2a** (R = Ac) and a halogen-free fraction of flaky crystals (200 mg.); m.p. 200–202° (from acetone), α_D −155°, $\lambda^{cyclohexane}$ 227 mμ (ϵ 6000), τ 8.0 (3H, acetate methyl), 4.8 (2H, side-chain olefinic protons), and 4.6 (1H, C-7 proton).

Anal. Calcd. for $C_{31}H_{48}O_2$ (452.69): C, 82.24; H, 10.68. Found: C, 81.93; H, 10.59.

5α,6α-Methylene-Δ$^{8(14)}$-ergosten-3β-ol Acetate.—Hydrogenation of **3a** (R = Ac, 218 mg.) over palladium on carbon (10%, 105 mg.) in ethyl acetate (50 ml.) at room temperature and atmospheric pressure for 24 hr. resulted in saturation of the side-chain double bond and migration of the 7,8 double bond to the 8,14 position. Recrystallization of the product from acetone gave flakes (150 mg.), m.p. 150–152°, no ultraviolet maximum above 210 mμ, τ 9.7 (cyclopropyl methylene protons), no n.m.r. signal for olefinic protons. The product gave positive tetranitromethane and Tortelli–Jaffé color tests.

5α,6α-Methylene-Δ$^{8(14),22}$-ergostadien-3β-ol Acetate.—Passage of dry hydrogen chloride through a chloroform solution of **3a** (R = Ac, 0.4 g. in 40 ml.) at room temperature for 2 hr. produced a deep violet color. The solution was poured onto ice-cold saturated sodium bicarbonate solution and extracted with chloroform, and the solvent was evaporated. The product, a semisolid (0.4 g.), showed in the ultraviolet spectrum a weak absorption around 250 mμ and gave a positive halogen test. Repeated chromatography and recrystallizations from acetone–methanol afforded halogen-free flakes (0.25 g.); m.p. 155–157°, no ultraviolet maximum above 210 mμ, τ 4.8 (2H, side-chain olefinic protons) and a complex absorption around τ 9.7 (cyclopropyl methylene protons). The product gave positive tetranitromethane and Tortelli–Jaffé tests.

Anal. Calcd. for $C_{31}H_{48}O_2$ (452.69): C, 82.24; H, 10.68. Found: C, 82.25; H, 10.68.

Noncatalytic Dehalogenation of 5α,6α-Dihalomethylene Adducts. A. With Lithium Aluminum Hydride. A solution of the dibromo adduct **2a** (R = C_5H_9O, 2.5 g.) in anhydrous diethyl ether (250 ml.) was magnetically stirred with powdered lithium aluminum hydride (2 g.) for 2 days. Excess $LiAlH_4$ was cautiously destroyed with 5% aqueous sodium hydroxide. The coagulated white solid was filtered off and the ether filtrate was evaporated. Hydrolysis of the resulting adducts to the alcohols and acetylation gave a halogen-free product (1.6 g.), m.p. 110–120°. Chromatography over alumina gave, in the early fractions, 5α,8α-methylene-Δ^{6,22}-ergostadien-3β-ol acetate (**9a**); 1.4 g., m.p. 129–130° (from acetone–methanol), no ultraviolet maximum above 210 mμ, τ 4.8 (2H, side-chain olefinic protons) and a quartet around τ 4 (2H, 6,7 double bond protons).

Anal. Calcd. for $C_{31}H_{48}O_2$ (452.69): C, 82.24; H, 10.68. Found: C, 82.08; H, 10.51.

Later chromatographic fractions contained 5α,6α-methylene-Δ^{7,22}-ergostadien-3β-ol acetate (**3a**, R = Ac).

Treatment of a solution of the 5α,6α-dichloromethylene adduct of ergosteryl tetrahydropyranyl ether (1 g.) in anhydrous diethyl ether (100 ml.) with $LiAlH_4$ (1 g.) for 2 days gave a halogen-containing product. Repeated chromatography of the acetate afforded the 5α,6α-methylene adduct **3a** (0.2 g.) and halogen-containing fractions. However, when the dichloro adduct (1 g.) in dry tetrahydrofuran was refluxed with $LiAlH_4$ for 2 days, a product which gave a faint halogen test (sodium fusion) was obtained. Repeated chromatography of the acetate gave equal amounts of 5α,6α- and 5α,8α-methylene adducts (*ca.* 0.2 g. each).

Reduction of 5α,6α-dibromomethylene adduct (1 g.) with lithium aluminum deuteride (1 g., Metal Hydrides) in anhydrous ether as described above gave the 5,8-dideuteriomethylene

taken in alcohols or in cyclohexane on a Cary recording spectrophotometer Model 11M. N.m.r. spectra were taken on a Varian A-60 instrument. Concentrations of 10–15% in deuteriochloroform or carbon tetrachloride were used. Positions of peaks are relative to tetramethylsilane at τ 10.0. Optical rotations were measured in chloroform solutions at concentrations of 1.5–2% in a 1-dm. tube. Chromatograms were conducted on Woelm neutral alumina. Analyses were carried out by Dr. S. N. Nagy at the Massachusetts Institute of Technology.

(42) See ref. 37, p. 119.

(43) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

adduct (0.5 g.); m.p. 129–130°, τ 4.8 (2H, side-chain olefinic protons) and a quartet around τ 4 (2H, 6,7 double bond protons).

B. With Lithium in *t*-Butyl Alcohol–Tetrahydrofuran.—To a mechanically stirred solution of the dibromomethylene adduct **2a** (R = C_5H_9O, 2.8 g.) in dry tetrahydrofuran (50 ml.) were added lithium flakes in portions (total of 3 g. over a period of 6 hr.) and *t*-butyl alcohol (50 ml., distilled over potassium) dropwise. At the end of the reaction period, the mixture was poured over ice and the resulting precipitate was filtered. The product (2.0 g.) gave a negative halogen test. Hydrolysis, acetylation, and initial recrystallization from ethyl acetate–methanol afforded 1.52 g. of flakes, m.p. 195–197°. Repeated chromatography gave the 5α,6α-methylene adduct **3a** (R = Ac), m.p. 200–202°.

Slow evaporation of the mother liquor from the initial recrystallization of the acetate left 0.16 g. of long needles, m.p. 120–124°. Recrystallization from acetone–methanol afforded an analytical sample of the 5α,8α-methylene adduct **9a** (R = Ac), m.p. 129–130°.

C. With Sodium in Liquid Ammonia.—A solution of the 5,6-dibromomethylene adduct **2a** (R = C_5H_9O, 2.8 g.) in dry diethyl ether (150 ml.) was added to a magnetically stirred and Dry Ice cooled solution of sodium (2.9 g.) in anhydrous liquid ammonia (200 ml.). After 6 hr., the blue color was discharged by the addition of solid ammonium chloride, and the ammonia was allowed to evaporate. Extraction of the product with ether and evaporation of the ether afforded a halogen-free solid which was hydrolyzed and acetylated. The acetate was separated, as previously described, into 5α,6α-methylene adduct **3a** (1.75 g.) and 5α,8α-methylene adduct **9a** (0.17 g.).

Catalytic Hydrogenation of 5α,8α-Methylene Adduct 9a (R = Ac).—A solution of the title compound (0.5 g.) in ethyl acetate (30 ml.) was stirred with platinum oxide (100 mg.) under hydrogen at room temperature and atmospheric pressure for 12 hr. Filtration of the catalyst and evaporation of the solvent gave a solid (0.5 g.), m.p. 99–100° (from methanol); the n.m.r. spectrum showed no olefinic proton absorptions.

Anal. Calcd. for $C_{31}H_{52}O_2$ (456.73): C, 81.52; H, 11.48. Found: C, 81.21; H, 11.51.

Conversion of 5α,8α-Methylene-22,23-dihydride 10 to Diketones 13 and 14.—A solution of 5α,6α-dibromomethylene **2a** (R = C_5H_9O, 2 g.) in ethyl acetate (250 ml.) was shaken with 10% platinum on carbon under hydrogen (30 p.s.i.) at room temperature for 10 hr. Filtration of the catalyst and evaporation of the solvent left solid **10** (2 g.); $\lambda^{cyclohexane}$ 218 mμ (ϵ 9000), τ 4.6 (1H, C-7 proton) and no other olefinic absorptions in the n.m.r. spectrum. Hydrolysis to the alcohol and acetylation gave the corresponding acetate, m.p. 150–151° (from acetone–methanol).

Anal. Calcd. for $C_{31}H_{48}Br_2O_2$ (612.52): C, 60.13; H, 7.89; Br, 26.09. Found: C, 60.16; H, 7.83; Br, 26.16.

The hydrogenation product **10** (1 g.) was treated with lithium aluminum hydride as previously described. Hydrolysis to the alcohol **11** and acetylation gave 0.6 g. of acetate; m.p. 124–125° (from acetone–methanol), τ 4 (2H, 6,7 double bond protons), no ultraviolet maximum above 210 mμ.

Anal. Calcd. for $C_{31}H_{50}O_2$ (454.71): C, 81.88; H, 11.08. Found: C, 81.73; H, 10.99.

The alcohol (0.5 g.) was treated with monoperphthalic acid[44] in ether for 15 hr. The ethereal solution was washed with sodium hydroxide, dried, and evaporated. The epoxide (0.4 g.), acetate m.p. 138–139° (methanol), showed in the n.m.r. spectrum two doublets at τ 5.25 and 6.8 (epoxide protons).

Anal. Calcd. for $C_{31}H_{50}O_3$ (470.71): C, 79.10; H, 10.70. Found: C, 78.96; H, 10.66.

Treatment of the epoxide **12** (0.35 g.) with lithium aluminum hydride (0.2 g.) and oxidation of the resulting diols with 8 *N* chromic acid[45,46] (added dropwise to a solution of the alcohols in redistilled acetone) afforded a mixture of diketones **13** and **14** (0.2 g.); ν^{Nujol} 5.65, 5.70, 5.80, and 5.85 μ. Repeated chromatography gave in the early fractions a solid (0.1 g.); m.p. 176–178° (from aqueous methanol), ν^{Nujol} 5.70 and 5.80 μ.

Anal. Calcd. for $C_{29}H_{46}O_2$ (426.66): C, 81.66; H, 10.82. Found: C, 81.77; H, 10.76.

Later chromatographic fractions gave a glassy product (*ca.* 50 mg.) which showed infrared bands at 5.65 and 5.85 μ.

Conversion of the 5α,8α-Methylene Adduct to γ-Lactone 16.—Ozone was passed through a solution of adduct **15** (0.5 g.) in *n*-hexane (30 ml.) at 0° for 1 hr. The solution was concentrated under reduced pressure to about 5 ml., distilled water (50 ml.) was added, and the mixture was heated on the steam bath with 30% hydrogen peroxide (10 ml.) for 1 hr. The insoluble gummy product was dissolved in ether and extracted with 5% sodium hydroxide. The residue, after evaporation of the ether, was treated again with hydrogen peroxide and extracted with sodium hydroxide. The combined alkaline extracts were acidified with hydrochloric acid and ether extracted. Evaporation of the ether left an oily residue which was dissolved in methanol (50 ml.) and refluxed with hydrochloric acid (0.3 ml.) for 30 min. The volume of the solution was reduced to 10 ml. and water was added. The separated oil was extracted with ether and the residue, after evaporation of the ether, was esterified with diazomethane and chromatographed over alumina (grade II). The infrared spectra of the majority of fractions (oils) showed two bands in the carbonyl region: 5.65 (γ-lactone) and 5.75 μ (methyl ester). All fractions that showed the two carbonyl bands were combined and rechromatographed but no solids were obtained upon repeated chromatography; estimated lactone content, 150 mg. One fraction was dissolved in sodium hydroxide (5%) on the steam bath, cooled, covered with ether, and acidified with cold sulfuric acid (10%). The product, extracted with ether, lacked a γ-lactone band in the infrared spectrum. Treatment of this acidic product with a few drops of hydrochloric acid in methanol regenerated the lactone, as shown by its infrared spectrum.

Experiments with $\Delta^{5,7}$-Cholestadien-7-*d*-3β-ol.—The title compound was prepared by following procedures for the preparation of 7-dehydrocholesterol[22,23] with the exception of using lithium aluminum deuteride in place of lithium aluminum hydride. Starting with 35 g. of cholesterol only 3.5 g. of the diene were obtained; m.p. 146–148°; λ^{EtOH} 293, 282 (ϵ 11,500), 272, and 265 mμ. Treatment of the diene with dihydropyran and phosphorus oxychloride as previously described for the preparation of ergosteryl tetrahydropyranyl ether and chromatography of the product gave 2 g. of the corresponding tetrahydropyranyl ether; τ 6.4 (3H), 5.2 (1H), 4.6 (1H, C-6 proton).

The ether (2 g.), *n*-pentane (50 ml.), potassium *t*-butoxide (3 g.), and bromoform (2 ml. in 10 ml. of *n*-pentane) on reaction gave a noncrystalline bromine-containing product. Purification through chromatography gave oily fractions the n.m.r. spectra of which showed no olefinic protons; the ultraviolet spectrum had a band at 218 mμ.

A 0.8-g. portion of the bromine-containing product was treated with lithium aluminum hydride (1 g.) as previously described for the preparation of **9a**. Chromatography of the acetate gave a solid (150 mg.); m.p. 95–96° (from acetone–methanol), no ultraviolet maximum above 210 mμ, a singlet at τ 4 (1H, C-6 proton).

Anal. Calcd. for $C_{30}H_{47}DO_2$ (441.69): C, 81.57; H plus D, 11.18. Found: C, 81.57; H, 11.12.

Another portion (0.3 g.) of the bromine-containing oil was dissolved in dry ether (10 ml.) and added to a stirred solution of sodium (0.5 g.) in liquid ammonia (150 ml.) at Dry Ice temperature. The product, after the usual work-up, was a halogen-free oil which showed no olefinic protons in the n.m.r. spectrum, and had an ultraviolet band at 227 mμ.

$\Delta^{2,4}$-Cholestadiene. A. From Dehydration of Cholesterol.—Cholesterol (60 g.) was dehydrated over alumina according to the procedure of Skau and Bergman.[26] Distillation of the reaction mixture afforded 30 g. of product; m.p. 58–61°, α_D +80°. Recrystallization from diethyl ether at 0° gave $\Delta^{2,4}$-cholestadiene (20 g.); m.p. 60–92°, α_D +125°, $\lambda^{cyclohexane}$ 265 and 274 mμ.

B. From Cholestanone.[27]—Commercial cholesterol was purified through the dibromide[47] and hydrogenated to cholestanol according to the procedure of Hershberg.[48] Cholestanol was then oxidized to cholestanone,[49] m.p. 130–131°. Dibromination of cholestanone with bromine in acetic acid gave 2α,4α-dibromocholestanone,[50] m.p. 190–193°.

A solution of 30 g. of 2α,4α-dibromocholestanone and 30 g. of sodium iodide in 700 ml. of acetone was refluxed for 24 hr. The precipitate was filtered off and the color in the filtrate was dis-

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charged by the addition of sodium thiosulfate solution. An oil separated upon addition of ice–water to the acetone solution. Cooling in the refrigerator for several hours caused solidification of the oil. The solid was collected and dissolved in dioxane (350 ml.). Sodium borohydride solution (35 g. in 30 ml. of water) was added and the mixture was stirred at 5–15° for 24 hr. A solid separated upon addition of water and was collected and left to dry; yield, 20 g. of iodohydrin.

The iodohydrin (20 g.), zinc–copper couple[51] (65 g.), sodium acetate (30 g.), and glacial acetic acid (500 ml.) were mixed and stirred at 15–20° for 8 hr. The solids were filtered and washed with *n*-hexane, and the filtrate and washings were neutralized with sodium carbonate. The hexane solution was then dried and evaporated, and the solid was chromatographed over alumina (grade I). The chromatographic fractions contained 2.5 g. of $\Delta^{2,4}$-cholestadiene; m.p. 64–66°, α_D +145°, $\lambda^{cyclohexane}$ 265 (ϵ 6500) and 274 mμ.

Reaction of $\Delta^{2,4}$-Cholestadiene with Dihalocarbenes.—Generation of dibromocarbene as usual in the presence of $\Delta^{2,4}$-cholestadiene (10 g.) afforded an oil; $\lambda^{cyclohexane}$ no bands above 210 mμ, ν^{neat} 13.4 and 13.9 μ, τ 4.7 (1H, C-4 proton). Repeated chromatography gave in the early fractions an amorphous solid (8 g.); m.p. 109–110°, α_D +117°, ν^{KBr} 13.4 μ.

Anal. Calcd. for $C_{28}H_{44}Br_2$ (540.46): C, 62.22; H, 8.20; Br, 29.57. Found: C, 62.17; H, 8.07; Br, 29.53.

Repeated chromatography of the later fractions gave a crystalline solid (60 mg.), m.p. 113° (from ethyl acetate–methanol). The n.m.r. spectrum had complex absorption at τ 3.2–4, $\lambda^{cyclohexane}$ 283 mμ (ϵ 3500).

Anal. Calcd. for $C_{28}H_{43}Br$ (459.5): Br, 17.5. Found: Br, 17.80.

Reaction of $\Delta^{2,4}$-cholestadiene with dichlorocarbene gave after chromatography a solid, m.p. 90–93°, α_D +115°, the spectral properties of which corresponded to those of the dibromo adduct.

Dehalogenations of Adducts of $\Delta^{2,4}$-Cholestadiene.—The previously described procedures of dehalogenation were applied to the dibromo and dichloro adducts of $\Delta^{2,4}$-cholestadiene. In all cases the products were halogen-containing mixtures. Chromatography over alumina (grade I) separated the mixtures into two components. Yields were variable and depended on the length of time of the reaction. The halogen-free component was eluted first.

2α,3α-Methylene-Δ^4-cholestene (4b) had m.p. 118–119°, no ultraviolet maximum above 210 mμ, τ 4.6 (C-4 proton) and 10.1 (cyclopropyl methylene protons).

Anal. Calcd. for $C_{28}H_{46}$ (382.65): C, 87.88; H, 12.12. Found: C, 87.84; H, 12.01.

2α,3α-Monobromomethylene-Δ^4-cholestene had m.p. 134–135°, α_D +207°, τ 4.6 (1H, C-4 proton) and 6.6 (1H, C*H*Br).

Anal. Calcd. for $C_{28}H_{45}Br$ (461.56): C, 72.86; H, 9 83; Br, 17.31. Found: C, 72.92; H, 9.76; Br, 17.18.

2α,3α-Monochloromethylene-Δ^4-cholestene had m.p. 142–143°, α_D +217°, τ 4.6 and 6.6.

Anal. Calcd. for $C_{28}H_{45}Cl$ (415.1): C, 80.62; H, 10.88; Cl, 8.50. Found: C, 80.40; H, 10.98; Cl, 8.34.

$\Delta^{3,5}$-Cholestadiene.—Pyridinium cholesteryl sulfate,[52] prepared by the action of pyridine sulfur trioxide[53] on cholesterol, was converted to the potassium salt. To a refluxing solution of sodium capryloxide in capryl alcohol, prepared by dissolving sodium (3 g.) in capryl alcohol (700 ml., dried and distilled over anhydrous potassium carbonate), was added 18 g. of potassium cholesteryl sulfate. The mixture was refluxed for 2 hr. and the carpyl alcohol was removed by prolonged steam distillation. Upon cooling, the residual oil set to a solid mass which was filtered and washed with 95% ethanol. The yield of crude $\Delta^{3,5}$-cholestadiene[29] was 11 g. Crystallization from ethyl acetate–methanol gave 9 g. of the diene; m.p. 77–79°, α_D −122°.

3α,4α-Dihalomethylene Adducts and Their Dehalogenation Products.—Addition of dibromocarbene as previously described gave 3α,4α-dibromomethylene-Δ^5-cholestene (**5a**); m.p. 148–149°, α_D −29°, τ 4.7 (1H, C-5 proton).

Anal. Calcd. for $C_{28}H_{44}Br_2$ (540.46): C, 62.22; H, 8.20; Br, 29.57. Found: C, 62.64; H, 8.22; Br, 29.69.

Dichlorocarbene and $\Delta^{3,5}$-cholestadiene gave 3α,4α-dichloromethylene-Δ^5-cholestene; m.p. 143–144°, α_D −37°, τ 4.7 (1H, C-5 proton).

Anal. Calcd. for $C_{28}H_{44}Cl_2$ (451.5): C, 74.47; H, 9.82; Cl, 15.70. Found: C, 74.29; H, 9.74; Cl, 15.63.

Treatment of the dibromomethylene adduct **5a** with sodium in liquid ammonia or with lithium aluminum hydride gave 3α,4α-methylene-Δ^5-cholestene (**5b**); m.p. 108–109°, α_D −29°, τ 4.8 (1H, C-5 proton) and 9.9 (2H, cyclopropyl methylene protons).

Anal. Calcd. for $C_{28}H_{46}$ (382.65): C, 87.88; H, 12.12. Found: C, 87.75; H, 12.15.

Dehalogenation of the dichloro adduct with sodium in liquid ammonia or lithium aluminum hydride gave a mixture separable by chromatography into **5b** and 3α,4α-monochloromethylene-Δ^5-cholestene; m.p. 131–132°, τ 4.78 (1H, C-5 proton) and 6.7 (1H, C*H*Cl).

Anal. Calcd. for $C_{28}H_{45}Cl$ (415.1): C, 80.62; H, 10.88; Cl, 8.50. Found: C, 80.75; H, 10.80; Cl, 8.40.

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